II. Rejection under 35 U.S.C. §112, Second Paragraph

Claims 1-3. 6-7 and 18 are rejected under 35 U.S.C. §112, s
indefinite for failing to particularly point out and distinctly claim th
regards as the invention.

In claim 1, the phrase "treating a patient having a condition
metabolism during a systemic inflammatory response is desired" h
amended recites a method for conferring resistance to endotoxic sh
ligand, the terms of which are definite and have support in the spec
The alleging indefiniteness of the claim is now overcome.

Claim 18 has been amended to recite specific compounds w
OB-R expression. With the noted amendment, the rejection for ind

Claim 33 has been canceled. As such the rejections for ind
antecedent basis are no longer relevant.

In view of the above comments, along with the amendment
Applicants believe that the rejections for indefiniteness are overcor
request that the rejections on this ground for the pending claims be

III. Rejection under 35 U.S.C. §112, First Paragraph

1. Claims 1-3 and 6-7

Claims 1-3 and 6-7 are rejected under 35 U.S.C. §1
containing subject matter which was not described in the specificat
one skilled in the art to which it pertains, or with which it is most r
and/or use the invention. Applicants respectfully traverse this reje

The Examiner contends that the claim directed to a method
condition in which regulating energy metabolism during a systemi
accomplished with a OB-R agonist ligand is contrary to the treatm
Examiner believes that one should promote weight gain and not w

the steps of:

administering to the animal IL-6 in an amount from about 0.5 to about 20 micrograms per kilogram body weight; and

administering to the animal recombinant OB protein in an amount from about 1 microgram per kilogram body weight to about 50 micrograms per kilogram body weight.

C5 Cont

REMARKS

Claims 1-3, 6, 7, 18, 20-24, and 26-31 are now pending in view of the above amendments. Applicants maintain that no new matter is presented by the above amendments. The present response is believed to fully meet all of the objections and rejections set forth in the Action.

With regard to the comments, objections and rejections presented in the Action by the Examiner, Applicants' response continues below.

I. The Amendments

Claims 1-3, 6, 7, 18, 20-24, and 26-31 are presently pending. Claims 19, 25 and 33 have been canceled to promote administrative efficiency. The claim cancellations and amendments as made herein are without prejudice to Applicants' right to pursue the canceled subject matter in a timely-filed continuation application. In addition, the cancellations and amendments are expressly not to be construed as an abandonment of the subject matter or an acquiescence to any grounds for rejection that may be outstanding in this matter. Support for claim amendments include the following: 1) claim 1 - page 8, lines 27-29, and page 22, beginning at line 9 continuing to page 23, line 29, and Figure 11; 2) claims 6 and 7 - page 2, lines 21-28; 3) claim 18 - incorporated claim 19; and 4) claim 27 - page 20, lines 1-23 and Figures 1 and 5.

Applicants assert that no new matter has been introduced as a result of the amendments.

treatment in response to an inflammatory response. The Examiner incorrectly surmises that the desired result of the claimed method is anorexia.

Applicants direct the Examiner's attention to the specification on pages 22 to 24 and in particular to Figure 11 where treatment with an OB-R agonist ligand, in this case recombinant OB protein, in an animal with endotoxic shock induced by exposure to LPS resulted in **survival** of the animal. Treatment with OB protein allowed the mice to survive a higher dose of LPS that was fatal to animals receiving LPS alone. Regulation of energy metabolism in the animals was demonstrated by increased body temperatures coupled with less severe symptoms of endotoxemia, remaining alert and responsive to touch and other manipulation followed by a quick recovery. Thus, OB protein treatment conferred complete resistance to LPS-induced endotoxic shock by means of regulating energy metabolism. These animals that survived the endotoxic shock did ultimately exhibit weight loss compared to the control group but the goal was not to produce anorexic animals; rather, the goal was to stabilize and overcome endotoxic shock. Applicants contend that claim 1 was enabled to this end without any ambiguity. However, in an effort to promote prosecution and focus the claim on the survival aspect by conferring resistance to endotoxic shock, Applicants have so amended the claims and assert that enablement is provided by the teachings of the specification.

In view of the foregoing arguments or amendments, Applicants contend that the rejections have been overcome and respectfully request that the rejections be withdrawn directed to the pending claims 1-3 and 6-7.

2. Claims 18, 20-24 and 27

Claims 18, 20-24 and 27 are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants respectfully traverse this rejection.

The Examiner rejected claims 18 and 20-24 on the basis that the specification does not

enable treatment of obesity with any OB receptor expression inducer. The Examiner further contends that expression regulation is unpredictable. Applicants contend conversely that compounds including cytokines are well known to one of ordinary skill in the art and that such a person would consider the invention reasonably to include any molecule that is known or could readily be evaluated with the methods of the invention as described on specification beginning on page 16 continuing to page 19. The determination of a compound having the requisite activity is not undue. According to the courts, Applicants need not prepare and test each and every possible combination of compounds that could induce OB receptor expression encompassed by the claims. The relevant inquiry in determining whether a particular claim is supported by the specification is whether the specification contains sufficient teachings **regarding the subject matter of the claim** as to enable one skilled in the art to make and use the invention. *In re Moore*, 169 USPQ 236, 239 (C.C.P.A. 1971; emphasis added). Thus, if one were interested in performing an assay, for example, it would be within the purview of a skilled worker to consult the relevant art -- e.g., solid-phase assays -- to ascertain appropriate inducers for use as disclosed herein. Arguably, even if some experimentation is necessary, enablement is not precluded. *Atlas Powder Co. v. E. I. duPont de Nemours & Co.*, 224 USPQ 409, 413 (Fed. Cir. 1984).

Thus, Applicants argue that the claims 18 and 20-24 are enabled and supported by the teachings in the specification. However, to expedite prosecution and allowance of the claims, Applicants have amended claim 18 to recite specific compounds that are shown to induce OB-R expression as shown in the specification at page 20, lines 1-23 and in Figures 1 and 5. The induction of OB-R with treatment by the recited compounds in conjunction with treatment with an OB-R agonist ligand, such as OB protein, was shown in animal models to confer survival and ultimately cause weight reduction. As such, Applicants contend that the claims as presently pending are enabled.

The Examiner also rejects claims 27 for lack of enablement because the specification lacks a single example of the treatment of a patient by administration of IL-6 and OB protein. As discussed above, enablement is established if the specification provides illustrative examples to

teach those of ordinary skill how to make and use the invention. Such support for claim 27 is provided in the specification at page 23, lines 9-29. Thus, Applicants assert that the claim is enabled as originally written and as presently amended.

In view of the foregoing arguments or amendments, Applicants contend that the rejections have been overcome and respectfully request that the rejections be withdrawn directed to the pending claims 18, 20-24 and 27.

IV. Rejection under 35 U.S.C. §103(a)

Claims 18-26 and 28-31 are rejected under §103(a) as being obvious over Grunfeld et al. Applicants respectfully traverse this rejection.

The Examiner contends that Grunfeld et al. teach that "endotoxins and cytokines (related to inflammation and infection) induce expression of leptin/OB in response to infection" and therefore it would be obvious to one of ordinary skill in the art that OB is beneficial to the anorexic response and that the inflammatory endotoxins and cytokines enhance this response by inducing expression of endogenous OB.

Applicants first direct the Examiner to the specification on page 20, lines 1-23, where treatment with LPS as well as cytokines increases the expression of the OB receptor not OB as contended by the Examiner. Secondly, the amount of weight loss exhibited in the animal models of the present invention when exposed to an OB-R inducer in the presence of OB protein was greater than any other as reported in the literature (16% in the first 24 hours, compared with an average of 10% reported by other groups) as supported in the specification at page 15 , lines 2-11. Thus, the present invention provides unexpected advantages over any of the previous described uses of OB protein, particularly that of the cited art that neither teaches or suggests the present invention.

Therefore, coupled with Applicants' earlier arguments already of record along with those herein, Applicants contend that the rejection for obviousness is overcome. Applicants request that the rejection for obviousness be withdrawn in view of the absence of any teachings or

suggestions by Grunfeld et al. in encompassing the present invention as recited in claims 18-26 and 28-31.

V. Summary

Applicants believe that a complete response is provided in the foregoing amendments and remarks to each issue and grounds for rejection and objection raised by the Examiner. Applicants submits that patentable subject matter exists with regard to the pending claims and therefore respectfully requests favorable action and entry of the presents amendments and response. The application is now believed to be in proper condition for allowance and early notification of allowance is earnestly solicited. The Examiner is invited to telephone the undersigned if it would be deemed helpful to advance the application.

October 10, 2002
Date

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APPENDIX I

Please enter the amendments to claims 1, 6, 7, 18, 20, 21, 26 and 27 below.

1. (Amended) A method for [treating a patient having a condition in which regulating energy metabolism during a systemic inflammatory response is desired] conferring resistance to endotoxic shock, comprising administering to an animal a composition having a physiologically effective amount of at least one OB-R agonist ligand.

6. (Amended) The method of claim 1 wherein the [condition is] endotoxic shock occurs in sepsis.

7. (Amended) The method of claim 1 wherein the [condition is] endotoxic shock occurs in systemic inflammatory response syndrome.

18. (Twice Amended) A method for the treatment of a patient having obesity comprising the steps of:

administering at least one [therapeutic cytokine OB-R expression inducer] compound capable of inducing OB-R expression selected from the group consisting of LPS, IL-1α, IL-1β, TNF-α and IL-6; and

administering a physiologically effective amount of an OB-R agonist ligand.

20. (Amended) The method of claim 18 wherein the [OB-R expression inducer] compound and the OB-R agonist ligand are administered at [a] different times.

21. (Amended) The method of claim 18 wherein the [OB-R expression inducer] compound is administered in an amount from about 0.003 to about 20 micrograms per kilogram body weight.

26. (Amended) The method of claim [25] 18 wherein IL-6 is administered in an amount from about 0.5 to about 20 micrograms per kilogram body weight.

27. (Twice Amended) A method for [the treatment of a patient requiring induction of] inducing OB receptor expression in an animal, comprising the steps of:

administering to the animal IL-6 in an amount from about 0.5 to about 20 micrograms per kilogram body weight; and

administering to the animal recombinant [human] OB protein in an amount from about 1 microgram per kilogram body weight to about 50 micrograms per kilogram body weight.

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